In-hospital Major Cardiovascular Events between STEMI Receiving Thrombolysis Therapy and Primary PCI

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ABSTRAK

Tujuan: *untuk membandingkan kejadian kardiovaskular mayor pada penderita infark miokard akut dengan elevasi segmen ST (IMA-EST) yang mendapatkan terapi trombolisis dengan intervensi koroner perkutan (IKP) primer selama perawatan di rumah sakit.* ***Metode:*** *penelitian kohort retrospektif dengan melihat rekam medik penderita IMA-EST onset <12 jam yang dilakukan terapi trombolisis dan tindakan IKP primer di RS. Dr. Sardjito Yogyakarta mulai 1 Januari 2008 sampai dengan 31 Maret 2010. Luaran klinik utama adalah kejadian kardiovaskular mayor yaitu gabungan kematian sebab kardiovaskular, reinfark dan stroke selama perawatan di rumah sakit. Luaran klinik sekunder adalah angina pektoris pasca infark, gagal jantung, syok kardiogenik dan efek samping perdarahan.* ***Hasil:*** *dari 78 penderita yang mendapat terapi trombolitik dan 53 penderita yang dilakukan tindakan IKP primer ditemukan kejadian kardiovaskular mayor selama perawatan di rumah sakit tidak berbeda bermakna yaitu 10,3% vs. 9,4% (RR 1,09; 95% CI 0,33-3,55; p=0,87). Kejadian angina pektoris pasca infark adalah 7% vs. 3,8% (RR 2,51; 95% CI 0,50-12,60; p=0,24). Kejadian gagal jantung lebih tinggi dan berbeda bermakna pada terapi trombolitik (17,9% vs. 5,7%, RR 3,64; 95% CI 0,99-13,38, p=0,04) dengan penurunan risiko relatif 68,1% pada IKP primer. Kejadian syok kardiogenik tidak berbeda bermakna. Efek samping perdarahan mayor dan minor tidak berbeda bermakna.* ***Kesimpulan:*** *tidak ditemukan perbedaan bermakna kejadian kardiovaskular mayor antara IMA-EST yang diterapi trombolisis dan IKP primer selama perawatan rumah sakit. Kejadian gagal jantung akut lebih tinggi pada terapi trombolitik, dan IKP primer menurunkan risiko gagal jantung akut.*

Kata kunci: *kejadian kardiovaskular mayor, IMA-EST, IKP primer, trombolisis.*

ABSTRACT

Aim: *to compare the in-hospital major cardiovascular events between thrombolysis therapy and primary percutaneous coronary intervention (PCI) in patients with ST-elevation acute myocardial infarction (STEMI.* ***Methods:*** *the study design is retrospective cohort. Medical record of patients with STEMI onset <12 hour receiving thrombolysis treatment or primary PCI in Dr. Sardjito Hospital Yogyakarta between January 2008 and March 2010 are evaluated. The primary outcome is major cardiovascular events which comprise cardiovascular death, reinfarction and stroke during hospitalisation. The secondary outcomes are post infarction angina pectoris, heart failure, cardiogenic shock and bleeding.* ***Results:*** *among 78 patients with thrombolysis and 53 patients with primary PCI, in-hospital major cardiovascular events do not differ significantly (10.3% versus 9.4%; RR 1.09, 95%CI 0.33-3.55; p=0.87). Post infarction angina pectoris is 7% versus 3.8% (RR 2.51, 95%CI 0.50-12.60;*

p=0.24). The incidence of heart failure is significantly higher in thrombolysis (17.9% versus 5.7%; RR 3.64, 95%CI 0.99-13.38; p=0.04), primary PCI reduces 68.1% relative risk to develop acute heart failure in STEMI. The incidence of cardiogenic shock is not different. Major and minor bleeding do not differ significantly either. ***Conclusion:*** *the in-hospital major cardiovascular events between STEMI receiving thrombolysis therapy and primary PCI is not significantly different. Heart failure is significantly higher in thrombolysis therapy and the primary PCI reduces the risk.*

Key words: *major cardiovascular events, STEMI, primary PCI, thrombolysis.*

INTRODUCTION

Coronary heart diseases currently rank number one as the cause of death in developed countries, with acute myocardial infarction (AMI) as the most frequent clinical manifestation. In 2006, approximately 1.2 million new cases emerged.[1] Almost one third of AMI is diagnosed as AMI with ST segment elevation (STEMI). Between 25% and 35% AMI cases die before receiving medical treatment, with ventricular fibrillation as the main cause of death.[2] The improvement of medical facilities and advancement of intensive managements have reduced the mortality rate.[3] This especially occurs in STEMI due to the enhancement of early management with reperfusion strategies such as thrombolysis therapy or primary percutaneous coronary intervention (PCI).[3]

Thrombolysis therapy has limitations due to its contraindication in about 25% of cases, its failure in 15% and the reocclusion within 3 months in 25% of cases. This limitations can be overcome by primary PCI. However, primary PCI requires advance facility, skilled human resources and longer time-frame (door to procedure time).[4]

Extensive clinical research have been performed comparing the effectiveness of thrombolysis therapy and primary PCI. Most studies reveal the superiority of primary PCI over thrombolysis therapy in the reduction of major adverse cardiovascular events such as mortality, stroke and reinfarction.[5] However, the research mostly come from developed countries which pioneered the revascularisation procedures for STEMI. In developing countries, such as Indonesia, the primary PCI for STEMI is only recently introduced and routinely performed in hospitals with cath-lab facilities. Our hospital is one of the cardiac centers in this country which is capable of performing the procedure. In our hospital, primary PCI has been carried out routinely since 2008. However, no evaluation of the outcome has been performed yet.

In the present study, we evaluated and compared the in-hospital major cardiovascular events, i.e. the composite of death, reinfarction and stroke, between thrombolysis therapy and primary PCI in patients with STEMI onset <12 hour in Dr. Sardjito Hospital Yogyakarta, Indonesia.

METHODS

The study design was the retrospective cohort. The subjects were patients hospitalised in intensive cardiovascular care unit (ICCU) Dr. Sardjito Hospital with STEMI and received thrombolysis therapy or primary PCI. The medical record data of these patients were retrieved and evaluated from January 1, 2008 until March 31, 2010. Inclusion criteria were STEMI diagnosis, anginal pain onset before procedure <12 hour and receiving thrombolysis with full dose streptokinase (1.5 million Units within 1 hour) or primary PCI. STEMI was diagnosed based on angina type chest pain more than 30 minutes, ST segment elevation on ECG with ST segment elevates >2 mmV in 2 consecutive precordial leads or >1 mmV in 2 consecutive limb leads or the new LBBB and dynamic elevation of creatin kinase MB (CK-MB) or troponin.[6,7] Exclusion criteria were shock cardiogenic which cannot be overcome by primary PCI, end-stage renal disease and creatinin level >1.5 mg/dl.

From the patients who satisfy the inclusion and exclusion criteria, we documented the age, gender, pain onset, time from pain onset

to thrombolysis therapy or primary PCI, history of hypertension and diabetes mellitus, smoking status, haemoglobin level, lipid profile, previous infarction, stroke, stenting or balloon angioplasty, CABG, history of medications, clinical parameters on admission, haemodynamic disturbance based on Killip class and infarct location based on ECG.

Primary outcome of the study was major cardiovascular events, i.e. composite of cardiovascular death, reinfarction and stroke, during intensive hospitalisation in ICCU. Cardiovascular death was a death due to cardial process such as cardiogenic shock, cardiac arrest or death without any other causes. Reinfarction was repeated anginal type chest pain and changes in ECG (i.e ST-segmen elevation >2 mmV in 2 precordial leads or >1 mmV in limb leads or new Q wave in 2 consecutive leads and repeated elevation of normalized CKMB. Stroke was new permanent neurological deficit and/or the presence of cerebral hemorrhage or ischemic lesion. Secondary clinical outcomes are post-infarction angina, heart failure, cardiogenic shock and side effects of major and minor bleedings.

Statistics analysis was performed with SPSS version 15. Patient characteristics are compared with T test for numerical data and chi square test for categorical data. Clinical outcomes were analysed with bivariate analysis by cross tabulation chi square test (95% confidence interval) and multiple logistic regression analysis for various significant confounding variables.

This study was approved by ethic committee of Faculty of Medicine Universitas Gadjah Mada Yogyakarta.

RESULTS

From medical record data, we retrieved 136 patients with STEMI <12 hour who received reperfusion procedures. Thrombolysis therapy was performed in 80 patients, two of these patients are excluded because they did not receive full dose streptokinase. Primary PCI was performed in 56 patients, three of these patients are excluded because they suffered from cardiogenic shock. Of 78 patients with thrombolysis therapy, five patients (6.4%) have failed thrombolysis as indicated by no signs of >50% depression of ST segment within 1 hour after thrombolysis. Of 53 patients with primary PCI, forty-nine patients (92.4%) underwent stent placement, two patients (3.7%) had only balloon inflation and one patient (1.8%) had thrombus aspiration. Patient characteristics on admission and during hospitalisation in ICCU are shown in **Table 1**. The proportion of smoker, the use of anticoagulants and inferior wall infarction is significantly higher in patients with thrombolysis therapy. Posterior infarction is greater in patients receiving primary PCI. The time from admission to procedure (door to procedure time) is significantly longer in patients with primary PCI.

The proportion of in-hospital major cardiovascular events is not significantly different between patients receiving thrombolysis therapy and primary PCI (10.3% versus 9.4%; RR 1.09, 95%CI 0.33-3.55; p=0.87). The proportion of cardiovascular death between patients receiving thrombolysis therapy and primary PCI does not significantly differ. Reinfarction only occurs in one patient with thrombolysis therapy, while stroke occurs in two patients. Overall, no increased risk to develop in-hospital major cardiovascular events are detected in thrombolysis group.

After adjusting using logistic regression analysis which included several risk factors which significantly differ between patients receiving thrombolysis therapy and primary PCI, i.e. smoking, the use of anticoagulant, inferior infarct location, posterior infarct location, total cholesterol level, we found that the thrombolysis therapy did not increase the risk for in-hospital major adverse cardiac events.

The incidence of post infarction angina pectoris is almost 4 times higher in thrombolysis therapy as compared with primary PCI, however this difference is not statistically significant. The incidence of heart failure is significantly higher in thrombolysis therapy as compared to primary PCI. Furthermore, primary PCI is associated with 68.1% risk reduction of heart failure as compared to thrombolysis (p=0.04). The incidence of cardiogenic shock is not significantly different in thrombolysis therapy as compared to primary PCI (p=0.52).

Table 1. Characteristics of patients with STEMI receiving thrombolysis therapy and primary PCI in Dr. Sardjito Hospital from January 2008 to March 2010

Characteristics	Thrombolysis therapy (n=78)	Primary PCI (n=53)
Age (years), mean±SD	55.31±8.08	58.54±10.9
Gender, n(%)		
- Male	67(85.9)	46(86.8)
- Female	11(14.1)	7(13.2)
Hypertension, n(%)	31(39.7)	25(47.2)
Smoking, n(%)	50(64.1)	25(47.2)
Diabetes mellitus, n(%)	19(24.4)	12(22.6)
Previous myocardial infarction, n(%)	2(2.0)	5(9.4)
Previous PCI, n(%)	0(0)	3(5.7)
Previous stroke, n(%)	3(3.8)	3(5.7)
On-admission parameters, mean±SD		
- Systolic blood pressure (mmHg)	123.22±22.01	122.03±21.86
- Diastolic blood pressure (mmHg)	76.15±13.7	75.05±13.89
- Total cholesterol (mg/dl)	207.3±44.8	183.1±47.9
- LDL cholesterol (mg/dl)	141.7±40.1	121.68±41.58
- Random glucose (mg/dl)	184.9±113.2	168.7±58.0
In-hospital medications, n(%)		
- Aspirin	77(98.7)	53(100)
- Clopidogrel	76(97.4)	53(100)
- Aspirin + Clopidogrel	74(94.5)	53(100)
- Anticoagulants	74(94.5)	35(66.1)
- Beta blocker	20(25.6)	14(26.4)
- Calsium channel blocker	2(2.6)	3(5.7)
- ACE inhibitor/ARB	58(74.4)	43(81.1)
- Diuretics	19(24.4)	15(28.3)
- Nitrate	55(70.5)	33(62.3)
- Statin	70(89.3)	50(94.3)
- Insulin	20(25.6)	11(20.8)
Peak CKMB, mean±SD	137.9±88.2	125.8±123.7
Killip class, n(%)		
- I	60(76.9)	43(81.1)
- II	10(12.8)	6(11.3)
- III	4(5.1)	2(3.8)
- IV	4(3.1)	2(1.5)
Infarct location, n(%)		
- Anterior	37(47.4)	27(50.9)
- Anteroseptal	37(47.4)	27(50.9)
- Inferior	40(51.3)	18(34.0)
- Posterior	25(32.1)	6(11.3)
- Lateral	16(20.5)	12(22.6)
- Dextra	14(17.9)	5(9.11)
Pain onset (hour), mean±SD	4.4±2.4	4.8±3.9
Door to procedur time (minute), mean±SD	71.4±42.1	96.2±70.4

Table 2. The in-hospital major cardiovascular events in STEMI patients receiving thrombolysis therapy and primary PCI

Outcomes	Trombolysis (n=78)		Primary PCI (n=53)		RR	95% CI	p value
	n	%	n	%			
Major cardiovascular events	8	10.3	5	9.4	1.09	0.33-3.55	0.87
Cardiovascular death	5	6.4	4	7.5	0.83	0.21-3.28	0.80
Reinfarction	1	1.3	0	0	0.98	0.96-1.01	0.40
Stroke	2	2.6	3	5.7	0.43	0.07-2.71	0.36

Table 3. Logistic regression analysis with several risk factors for in-hospital major adverse cardiac events in patients with thrombolysis therapy as compared to patients receiving primary PCI

Risk factors	RR	95% CI	P value
Thrombolysis therapy	0.95	0.14-4.81	0.95
Smoker	1.43	0.36-5.55	0.60
Total cholesterol levels	0.99	0.97-1.00	0.40
Inferior infarct	0.13	0.06-1.63	0.16
Posterior infarct	1.55	0.29-8.16	0.59
Anticoagulant treatment	0.48	0.46-5.03	0.54

Based on age, the incidence of major cardiovascular events among patients >60 years old tends to be higher in those receiving thrombolysis therapy (23.3% versus 14.3%; RR 1.87, 95% CI 0.38-9.12; p=0.69).

The side effect of bleeding tends to be higher in patients receiving thrombolysis therapy as compared to primary PCI. The incidence of major bleeding is 1.3% in thrombolysis and 0% in primary PCI (RR 1.68, 95% 1.46-1.94; p=1), minor bleeding is 12.8% in thrombolysis and 3.8% in primary PCI (RR 3.75, 95% CI 1.46-1.94; p=0.12) and total bleeding is 14.1% in thrombolysis and 3.8% in primary PCI (RR 4.18, 95% 0.88-19.72; p=0.07).

DISCUSSION

This study showed that in-hospital major cardiovascular events in STEMI onset <12 hours did not differ significantly between patients receiving thrombolysis therapy and primary PCI. Adjusted with several confounding risk factors by logistic regression analysis also showed no significant difference. The incidence of cardiovascular death, reinfarction and stroke did not significantly differ either.

Previous studies, both clinical trials and cohort studies, which compared the effectiveness of thrombolysis therapy and primary PCI in STEMI showed different conclusions. Studies which show no significant difference between thrombolysis therapy and primary PCI are from Every et al.,[8] Le May et al.,[9] and Ribichini et al.[10] In contrasts, studies reported significantly increased major cardiovascular events in thrombolysis therapy compared to primary PCI are studies performed by Aversano et al.[11] which reported 16.8% versus 9.8% (p=0.03) in STEMI <12 hour, by Garcia et al.[12] which reported 17% versus 6.4% (p=0.01) in STEMI <5 hour, by GUSTO IIb trial[13] which reported 13.6% versus 9.6% (p=0.03) incidence of 30-day major cardiovascular events in STEMI <12 hours and by Widimsky et al.[14] which showed 23% versus 8% (p=0.02) incidence of 30-day mortality in

Table 4. Post infarction angina pectoris, heart failure and cardiogenic shock in STEMI patients receiving thrombolysis therapy and primary PCI

Outcomes	Trombolysis (n=78)		Primary PCI (n=53)		RR	95% CI	p value
	n	%	n	%			
Post infarction angina	7	9.0	2	3.8	2.51	0.50-12.60	0.24
Heart failure	14	17.9	3	5.7	3.64	0.99-13.38	0.04
Cardiogenic shock	3	3.8	1	1.9	2.08	0.21-20.55	0.52

STEMI <6 hours. Keeley et al.[5] performed a meta-analysis from 23 clinical trials in STEMI <12 hours and reported cardiovascular events were higher in thrombolysis therapy as compared to primary PCI (18% versus 8%, p<0.001).

The incidence of post infarction angina pectoris in this study was not significantly different between patients receiving thrombolysis therapy and primary PCI. Reduction of the incidence of post-infarction angina pectoris by primary PCI as compared to thrombolysis therapy have already been reported.[9,10,12,14] However, our study could not replicate the previous findings although we showed the tendency of risk reduction of post infarction angina pectoris among primary PCI.

Heart failure and cardiogenic shock after acute myocardial infarction are clinical manifestations of reduced left ventricular function, both systolic and diastolic functions.[15] They are derived from reduced contractile function in the infarcted area, infarct expansion and increased pressure on ventricular wall due to increased intraventricular blood volume. Many mediators and patomechanism occur in this vicious circle involving various organs such as heart, lung and kidney.[16] The patency of coronary artery after reperfusion will improve the left ventricular function and heart contractility which halt the vicious circle.[17] Therefore, successful reperfusion will reduce the incidence of heart failure and cardiogenic shock. In our study, the incidence of heart failure in thrombolysis patients is significantly higher and primary PCI reduces the risk of acute heart failure in about 68.1%. The risk of cardiogenic shock is also tended to decrease in primary PCI. However,the GUSTO IIb trial showed no significant difference of heart failure and cardiogenic shocks between the two arms.[13]

In this study, among elderly patients (age >60 years) the incidence of major cardiovascular events tend to be higher in thrombolysis therapy than in primary PCI. Primary PCI associates with reduced risk of 38.6% among elderly. Grines et al.[18] investigated high-risk groups and found the incidence of 30-day cardiovascular events almost twice than low-risk groups. However, other study involving elderly >70 years showed no significant difference in major cardiovascular events.[19]

Adverse effect of bleeding, both major and minor bleeding, tends to be greater in thrombolysis. The incidence of major bleeding in thrombolysis therapy is 1.3%, whereas no bleeding is observed in primary PCI. Minor bleeding in thromboysis therapy is almost four-times as compared to primary PCI, but this is not significant. As a whole, total bleeding is slightly higher by the factor of four in thrombolysis therapy. The result is similar with other previous studies.[10,11,13,14]

Several limitations are observed in this study. The first is the relatively small sample size that reduce the power to detect significant differences between groups. The second is the nature of the study design which involves many biases in the selection of patients and the allocation for revascularisation procedure.

CONCLUSION

The study showed no significant difference on the incidence of in-hospital major cardiovascular events in STEMI onset <12 hours between patients receiving thrombolysis therapy and primary PCI The incidence of post-infarction angina pectoris, cardiogenic shock and events among elderly tend to be higher in thrombolysis therapy, primary PCI reduced risk of these events. In-hospital heart failure was significantly higher in patients receiving thrombolysis therapy and primary PCI reduced its relative risk.

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